REMARKS

Reconsideration is requested.

Claims 21-23 have been canceled, without prejudice.

Claims 1, 2 and 5-20 are pending. Claims 7, 11-14, 17 and 18 have been withdrawn from consideration.

Claim 1 has been revised, without prejudice, to define further patentable aspects of the disclosed invention. The applicants believe that amended claim 1 further distinguishes the claimed invention from the Examiner's interpretation of Schmidt (U.S. Patent No. 4,698,387) (i.e., "The macromolecular agent [of Schmidt] is chemically linked with an adduct ligant, thereby binding hemoglobin by way of a non-covalent bond."). No new matter has been added.

The specification has been amended to obviate the new matter rejection. The amendments have been made in a manner which is believed to comply with Rule 121(b)(1)(i) and (iv) and Rule 121((b)(2)(ii). The Examiner is requested to advise the undersigned, preferably by telephone, however if anything further is required in this regard. Withdrawal of the objection to the specification is requested.

Claims 21-23 have been canceled, without prejudice, to reduce the issues by making moot the Section 112, first paragraph "written description", rejection of claims 21-23. Withdrawal of the rejection is requested.

To the extent not obviated by the above amendments, the Section 103 rejection of claims 1, 2, 5, 6, 8-10, 15, 16 and 19-23 over Chauvierre (U.S. Patent Application Publication No. 2004/0028635) and Schmidt (U.S. Patent No. 4,698,387), and Desai

(U.S. Patent No. 6,096,331), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing comments.

The claimed invention requires a particle, with a specific structure, wherein the core of the particle is specifically defined and the surface of the particle is specifically defined. The Examiner's new reliance on Schmidtis believed to be misplaced as the patent fails to teach a particle of the invention and, with the Examiner's interpretation of the patent, the polysaccharide "macromolecular agent" of Schmidt would not be on the surface of the any particle alleged to be formed by Schmidt. Specifically, Schmidt teaches a structure whereby an "adduct" is non-covalently bound to hemoglobin. The "adduct" is formed from a "macromolecular agent", which the Examiner equates to the polysaccharide of the present claims, bound to an "anionic ligand". The "anionic ligand" of Schmidt's "adduct" is non-covalently bound to hemoglobin. Schmidt therefore fails to teach or suggest a particle structure of the claims wherein hemoglobin, for example, is non-covalently associated to a surface of a particle wherein the surface of the particle consists essentially of a polysaccharide or oligosaccharide. Any particle formed by Schmidt or suggested by Schmidt would presumably not have a surface portion required by the structure of the presently claimed invention.

The combination of cited art would not have made the claimed invention obvious.

The claims have been revised, without prejudice, in response to the Examiner's comments on page 7 of the Office Action dated April 8, 2009.

The Examiner's confirmation that Desai et al do not disclose that hemoglobin may be present in the polymeric shell of a heparin-coated particle, thereby providing a blood substitute, is acknowledged[1].

One of ordinary skill in the art will understand that compounds may associate non-covalently, as opposed to, for example, covalent attachments or associations. The distinction is important and significant in view of the art relied upon by the Examiner. Specifically, the cited Desai patent fails to describe "the ultrasonic irradiation process described above" or further describe how hemoglobin is to "participate in the delivery of a biologic".

The cited Desai patent however is a continuation-in-part of U.S. Patent No. 5,916,596, which is a continuation-in-part of U.S. Patent No. 5,665,382. Each of the parent patents are incorporated-by-reference in the cited Desai patent.

U.S. Patent No. 5,665,382, (herein after Grinstaff) describes and claims methods of preparing pharmaceutically active agents for in vivo delivery. The claimed method of Grinstaff involves cross-linking disulfide bonds of a biocompatible material with high intensity ultrasound to form a polymeric shell of the crosslinked material which contains a pharmaceutically active agent **in** the polymeric shell. See claim 1 of Grinstaff for example.[2] The cross-linking reaction of Grinstaff, and by incorporation Desai, is a

[1] See Advisory Action dated November 23, 2007 and page 10 of the Office Action dated June 23, 2008 ("Desai et al taught the synthesis of nanoparticles comprising synthetic block copolymers (column 10, lines 3-22), attached to biocompatible materials, i.e. polysaccharides (column 9, lines 42-49). Desai et al do not explicitly disclose heparin as a contemplated polysaccharide; however, absent evidence to the contrary, the art recognizes that heparin is a polysaccharide. Desai et al also contemplate that hemoglobin would be present in the polymeric shell (column 9, line 54; column 11, line 63), thereby providing a blood substitute.")

[2] The fact that the presently claimed invention allows for inclusion of active material in the recited particle does not suggest that it would have been obvious from the art to have associated a hemoprotein

covalent attachment which is distinct from and would have made obvious the non-covalent association of the presently claimed invention.

Claim 4 of Grinstaff specifically includes hemoglobin as a protein biocompatible material containing cross-linkable disulfide bonds which may be used to form a polymeric shell of Grinstaff. Claim 3 of Grinstaff alternatively states that "polysaccharides containing sulfhydryl groups and/or disulfide groups" may be biocompatible materials which may be used to form a polymeric shell of Grinstaff.

The cited Desai patent therefore, in referring to hemoglobin in the passages of column 11 of the Desai patent reproduced in the applicants previous Remarks, will be understood by one of ordinary skill in the art to be a reference to a polymeric shell formed of cross-linked hemoglobin. Alternatively, the cited Desai patent will be understood, from the whole of the patent and its incorporated-by-reference parent patent (i.e., Grinstaff), to relate to a polymeric shell formed of cross-linked polysaccharides containing disulfide or sulfhydryl groups.

Schmidt teaches that cross-linked hemoglobin is not ideally suited for physiological uses. See columns 1 and 2 of Schmidt.

Neither Desai nor Grinstaff teach or suggest a polymeric shell formed of cross-linked hemoglobin "coated with" (see Advisory Action dated November 23, 2007) or associated with heparin or any other saccharide or polysaccharide. Neither Desai nor Grinstaff teach or suggest a polymeric shell formed of cross-linked polysaccharides containing sulfhydryl groups associated with a protein, such as hemoglobin. The

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non-covalently with the surface portion of the particle as appears to be asserted by the Examiner. See

Examiner will appreciate that heparin is not a saccharide or polysaccharide containing sulfhydryl or disulfide groups[3], as would be required according to the teachings of Grinstaff and Desai to form a polymeric shell with high intensity ultrasound.

Moreover, Grinstaff further describes the aim and purpose of Desai's brief mention of hemoglobin polymeric shells in the following passage from column 19, line 22 through column 21, line 4 of Grinstaff reproduced in the Remarks of the applicants previous submission, which will be understood by one of ordinary skill in the art to clarify the vague reference in Desai to the use of hemoglobin polymeric shells as specific targeting or delivery agents. Specifically, Desai lists "physiologically active gasses", among the following broad genus of "biologic[s]" which may be delivered by the particles of polymeric shells (see column 9, lines 17-27 of Desai (as obtained from www.uspto.gov):

> As used herein, the term "biologic" refers to pharmaceutically active agents (such as analgesic agents, anesthetic agents, anti-asthamatic agents, antibiotics, anti-depressant agents, anti-diabetic agents, anti-fungal agents, anti-hypertensive agents, anti-inflammatory agents, anti-

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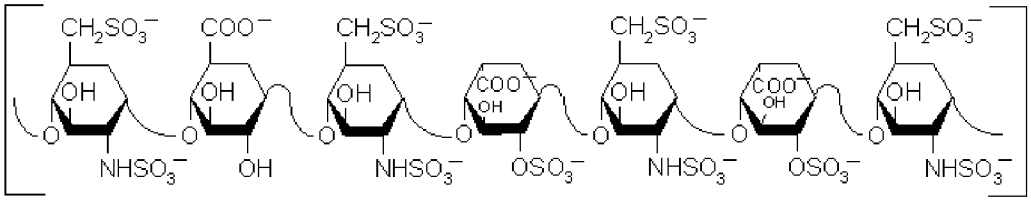
pages 9 and 10, for example, of the Office Action dated June 23, 2008.

[3] Heparin is a mucopolysaccharide with a molecular weight ranging from 6,000 to 40,000 Da. The average molecular of most commercial heparin preparations is in the range of 12,000 - 15,000. The polymeric chain is composed of repeating disaccharide unit of D-glucosamine and uronic acid linked by 1->4 interglycosidic bond. The uronic acid residue could be either D-glucuronic acid or L-iduronic acid. (Structure below) Few hydroxyl groups on each of these monosaccharide residues may be sulfated giving rise to a polymer with that is highly negatively charged. The average negative charge of individual saccharide residues is about 2.3.

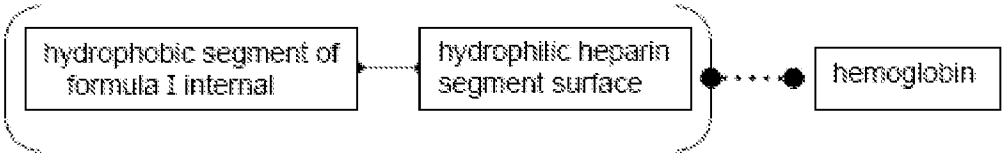


http://www.people.vcu.edu/~urdesai/hep.htm#Heparin%20-%20Structure

> neoplastic agents, anxiolytic agents, enzymatically active agents, nucleic acid constructs, immunostimulating agents, immunosuppressive agents, physiologically active gases, vaccines, and the like), diagnostic agents (such as ultrasound contrast agents, radiocontrast agents, or magnetic contrast agents), agents of nutritional value, and the like.

The description in Grinstaff to the use of particles of hemoglobin crosslinked polymeric shells containing oxygen to deliver oxygen is consistent with, and further explains, the aim and intent and teaching of Desai in the only two instances where hemoglobin is mentioned as a crosslinkable material of the polymeric shell of Desai's particles.

The Examiner is again urged to appreciate that the presently claimed invention provides a product of nanoparticles which include a sequenced block polymer with a particle core consisting essentially of the hydrophobic segment of formula (I), and a heparin saccharide hydrophilic segment, for example, at the surface of the particle, which is in turn associated with hemoglobin at the surface of the particle. This structure may be simply illustrated, without limitations, as the following linear representation of a component of the claimed nanoparticles, wherein the structure in brackets forms the nanoparticles and the hemoglobin is associated with the surface which contains the hydrophilic heparin:



In contrast to the above non-limiting schematic of an embodiment of the presently claimed invention, Desai teaches a particle shell of preferably crosslinked albumin or other disulfide or sulfhydryl containing proteins, such as hemoglobin (as further elucidated by Grinstaff which is incorporated-by-reference in Desai), which may be used as a targeting agent for chemotherapeutic drugs or encapsulated oxygen (in the case of crosslinked hemoglobin polymeric shells). Neither Desai nor Grinstaff teach or suggest nanoparticles made of polymeric shells containing a combination of a sequenced block polymer of formula (I) of the present claims covalently linked to a saccharide, such as heparin, in a particle shell, which is non-covalently associated with a hemoprotein, such as hemoglobin.

For reasons which are of record, the applicants submit that, in the case of hemoglobin, Desai describes cross-linked hemoglobin as a cross linked particle shell and that it would have been contrary to Desai to have non-covalently associated hemoglobin to a shell of a particle containing a saccharide hydrophilic segment.

Desai, at best, teaches the production of particles of crosslinked albumin, or other disulfide- or sulfhydryl-containing proteins (or disulfide- or sulfhydryl-containing saccharides such as hemoglobin) for delivery of encapsulated chemotherapeutics (or encapsulated oxygen in the case of the crosslinked "megameric" hemoglobin particles of Desai as elucidated by Grinstaff). Desai and Grinstaff teach that nanoparticles of Desai are, in one embodiment, crosslinked hemoglobin as hemoglobin contains cross-linkable sulfhydryl or disulfide groups and can be used not only to administer encapsulated oxygen but can also be used to transport oxygen in vivo as the ultrasonic

crosslinking method of Desai/Grinstaff allegedly does not substantially diminish the native oxygen-exchange capacity of the hemoglobin.

The Examiner has appreciated that nanoparticles of a sequenced block polymer of formula (I) of the present claims covalently linked to a saccharide were known in the art.[4] More specifically, the Examiner appreciates that Chauvierre describes nanoparticles of the claims.[5] The present specification further refers to Chauvierre in describing the particles of the present claims.[6]

With respect to the structure of the nanoparticles of the present invention, which the Examiner understands to have been known in the art, Chauvierre teaches that (emphasis added): [7]

> [0039] In the specific case of particles and micelles, it is probable that the copolymer has a structure arranged as follows: the chains of the same nature, that is to say saccharide or hydrophobic chains, group together, either to form the core structure of the micelle or particle or the brush-like ring around this core structure. Their distribution between the core structure and the ring will, of course, depend on the nature, aqueous or organic, of the solvent in which the particles or micelles are dispersed. The term "brush-like ring" is intended to denote a structure in which the segments constituting the ring are bonded via one of their ends to the segments constituting the core. Their free ends constitute the periphery of the ring. Thus, in aqueous medium, the hydrophobic segments are grouped together so as to form the core and the segments of saccharide nature are positioned in a brush-like ring all around this core. In a

[4] See page 10, ¶ ii) of the Office Action dated June 23, 2008.
[5] See page 5 of the Office Action dated June 23, 2008 ("Chauvierre et al teach the synthesis of nanoparticles of Inm to Imm [0045-46] comprising a core portion and a surface portion forming a sequenced block copolymer, said core portion comprising at least one hydrophobic segment having the formula as taught in Formula I, wherein "X" may be a "CN" moiety, wherein the hydrophobic segment may be a poly(alkylcyanoacrylate) [0010-0019], [0039] [0043-44] conjugated to a saccharide hydrophilic that may be heparin [0028].")
[6] See page 3, lines 20-29 of the present specification.
[7] See reproduction of US 2004/0028635 available at www.uspto.gov.

> solvent or organic type, this arrangement between the two types of segment is reversed: the core is of hydrophilic nature and is thus formed of the segments of saccharide nature and the brush-like ring is of hydrophobic nature and is thus formed of the segments of general formula (I).

Moreover, Chauvierre teaches that the brush-like structure of the particles of the present claims are distinguished from, for example, nanoparticles based on amphiphilic block copolymers comprising dextran and poly(alkyl cyanoacrylate) segments derived from the anionic polymerization of cyanoacrylate monomers in the presence of dextran, which have grafted structures. Such grafted structures had been previously described by S. J. Douglas et al.; Journal of Controlled Release (1986), 15-23).[8]

The copolymers of the present invention are distinguished from grafted structure of the prior copolymers in that the grafted structures can not contain the brush-like ring structure in an aqueous medium as several hydrophobic segments are covalently bonded to a single chain of saccharide nature.[9] Chauvierre teaches that the block form of the copolymers distinguish the copolymers of the claims and provide the particles of the claims with their definative structure. More specifically, Chauvierre describes as how the block form of the claimed copolymer is inaccessible by the previously used anionic polymerization.[10] One of ordinary skill in the art will appreciate from, for example, Chauvierre that the block structure of the claimed particles do not include side branches of saccharide nature on the hydrophobic segment or side branches of

[8] See ¶[0005] of Chauvierre.
[9] See ¶[0040] of Chauvierre.
[10] See ¶[0006] - [0009] of Chauvierre.

hydrophobic nature on the segment of saccharide nature, as would be found in a grafted structure.[11]

The claimed structure will be understood to inherently contain the "brush-like" structure, as described by Chauvierre.

The non-covalent association of a hemoprotein with a surface portion of the particles of the invention, as claimed, would not have been obvious from the cited combination of art.

It is this "brush-like" structure inherent to the claimed structure that confers to the nanoparticles the long circulating life that is essential for their application as blood substitutes. There was no reasonable or predictable expectation of success from the cited references, or from the general knowledge in the art, that the surface properties of the nanoparticles, in particular their long- circulating life in blood, would not be negatively impacted if they were associated with hemoglobin.

The inventors demonstrated that the biding of haemoglobin to the heparin coated nanoparticles did not affect the spectral properties of the haemoprotein, since the main characteristic peaks of haemoglobin CO were still present. These spectral characteristics together with the fact that the haemoglobin loaded heparin coated nanoparticles turned to the typical red color of haemoglobin after reduction with sodium dithionite and equilibration with CO were good indicators that haemoglobin maintained its capacity to exchange gas. Finally, results of zeta potential and of complement

[11] See ¶[0018] of Chauvierre. See also Bertholon et al. "Properties of Polysaccharides Grafted on Nanoparticles Investigated by EPR" Langmuir 2006, 22, 5485-5490; and Bertholon et al. "Characterization of Dextran - Poly(isobutylcyanoacrylate) Copolymers Obtained by Redox Radical and Anionic Emulsion Polymerization" Macromolecules 2006, 39, 3559-3567 (copies submitted herewith).

activation performed on the nanoparticles loaded with haemoglobin showed that the association of haemoglobin with the nanoparticle surface did not change the surface properties of the carrier, in terms of their zeta potential and of their complement activation properties, that are essential to define the fate of the nanoparticles m vivo after intravenous administration.[12]

These results are unexpected in view of, for example, the Desai patent, as elucidated by Grinstaff, which describes the unpredictability of hemoglobin-containing blood substitutes. Specifically, Grinstaff is believed to teach the importance of highly cross-linked hemoglobin polymer particles which is not required by and would be contrary to the presently claimed invention. Schmidt fails to cure these deficiencies.

Similarly, there was no reasonable or predictable expectation of success that the hydrodynamic radius of these nanoparticles would not be negatively affected by association of hemoglobin at their surface. The inventors demonstrated that the size of nanoparticles containing heparin was not significantly affected by the association of hemoglobin.[13] Moreover, there was no reasonable or predictable expectation of success that the associated hemoglobin would retain its capacity of transporting gases such as oxygen or carbon monoxide. The inventors have demonstrated that hemoglobin associated with the particles, as claimed, is functional.

Finally, there was no reasonable or predictable expectation of success that the particles of the invention non-covalently associated with a hemoprotein would not

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[12] See Chauvierre et al. Cell. Molec. Biol., 2004, 50(3), 233-239 "A New Generation of Polymer Nanoparticles For Drug Delivery" (of record).

[13] See Chauvierre et al, Biomaterials, 2004, 25, 3081-3086 "Heparin coated poly(alkylcyanoacrylate) nanoparticles coupled to hemoglobin: a new oxygen carrier" (of record).

activate complement. In fact, the applicants believe it would have been reasonable to expect that a hemoprotein associated with a surface saccharide of a particle would activate complement. The applicants believe the previously-submitted Andersson et al[14] demonstrates an expectation that the nascent C3b molecule of the complement pathway is able to bind specifically to proteins and carbohydrates via free hydroxyl or amino groups, forming covalent ester or amide bonds, respectively. The applicants believe that one of ordinary skill in the art would have expected that the either or both of the carbohydrates, such as dextran, or hemoproteins of the surface of the particles of the claims would activate complement. The applicants have demonstrated however that particles of the claims do not activate complement.

The claimed invention provides unexpected and surprising advantages which are persuasive evidence that the claimed products would not have been obvious in view of the cited combination of art.

The claims are submitted to be patentable over the cited combination of art. Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

[14] Andersson et al "Binding of C3 fragments on top of adsorbed plasma proteins during complement activation on a model biomaterial surface" Biomaterials 26 (2005) 1477-1485.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /B. J. Sadoff/
B. J. Sadoff
Reg. No. 36,663

BJS:
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100